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Dr. Veen and Colleagues Reply

TO THE EDITOR: We are grateful to Mr. Wade for his interest in and comments on our article. He is right to underline the strong association between younger age and use of cannabis. As a consequence, one should be cautious in assuming that the association between cannabis use and age at a first psychotic episode is causal. However, our research has suggested that the association was specific for the age at first psychotic episode because the impact of cannabis use on age at first social or occupational dysfunction was not significant. On that account, we have suggested that cannabis use may cause or contribute to a younger age at the first psychotic episode.

We also appreciate the interest of Dr. Krebs and colleagues in our study. The suggestion of an individual sensitivity to cannabis is interesting, and we would welcome further studies that examine this issue. However, we do not agree with the suggestion made by Dr. Krebs et al. that their findings contradicted our results. First, it remains unclear whether the samples they examined were representative of schizophrenia patients in general. Second, the authors do not state whether they adjusted the differences in age at onset between cannabis-sensitive patients and the remaining patients (or between cannabis users and nonusers) for gender. Finally, since the findings reported by Krebs et al. are significant (p=0.04) or almost significant (p=0.07), they seem to support, rather than contradict, our findings.

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Omega-3 Fatty Acids and Depression

TO THE EDITOR: In a recent issue of the *Journal,* Reeta Hakkarainen, M.B., et al. (1) failed to find an association between baseline intake of fish or dietary omega-3 polyunsaturated fatty acids and the risk of self-reported depressed mood or hospitalization for major depression during the 9-year follow-up of a prospective interventional cohort of male Finnish smokers (the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study). These results are conflicting with other studies (2–4), in particular, a cross-sectional study in Finland reporting a higher risk of depression in infrequent fish consumers (2). Two important points, however, were missed in the study by Dr. Hakkarainen et al.

First, clinical trials have suggested the antidepressive effects of long-chain omega-3 polyunsaturated fatty acids, especially eicosapentaenoic acid (5). Dietary alpha-linolenic acid can be converted to eicosapentaenoic acid but only at a very low rate. Main direct sources of long-chain omega-3 polyunsaturated fatty acids are fish, seafood, and fish oil. Was fish oil supplement use recorded in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study cohort?

Second, systemic oxidant stress due to tobacco use decreases blood polyunsaturated fatty acids, especially omega-3 long-chain polyunsaturated fatty acids, and increases lipoperoxidation products (6). Supplemental vitamin E can partly counteract these effects (6). Thus, the effects of omega-3 polyunsaturated fatty acids in smokers possibly depend on their antioxidant status and antioxidant intake. Because the subjects in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study were given supplements of either vitamin E, beta-carotene, both, or a placebo during the follow-up, the presence and direction of an association between omega-3 long-chain polyunsaturated fatty acid intake and depression can depend on the intervention group. Therefore, it would perhaps be worth looking at the possible interaction of omega-3 fatty acid intake with vitamin E and/or beta-carotene intervention before concluding an absence of association with depression. The size of the sample (8,612 subjects with depressed mood) allows this more detailed analysis.

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Dr. Hakkarainen and Colleagues Reply

TO THE EDITOR: We appreciate Dr. Astorg's comments on our article. To answer his first question, we did record the use of fish oil supplements in the cohort. At baseline, 448 (1.5%) of the 29,133 participants reported the use of fish oil supplements. This use was, however, so infrequent that it did not allow for meaningful analysis of its association with the risk of depression.

To address the second comment, we have reported that the trial supplementation had no influence on subsequent self-reported depression or hospital treatment due to major

depressive disorder (1). This finding implies that alpha-tocopherol supplementation did not modify the association between the intake of omega-3 fatty acids and the risk of depression.

Our results disagree with some earlier findings about the association of dietary fish with depression. However, we also have cross-sectional data that were assessed at study baseline showing no link between the dietary intake of fish and the self-report of depressed mood (39.3 g/day for both participants with depressed mood and those with no symptoms). Taking these facts together, we still see that our conclusions were justified.

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Instability of Symptoms in Recurrent Major Depression

TO THE EDITOR: In a recent issue of the *Journal,* Maria A. Oquendo, M.D., et al. (1) attempted to characterize unipolar depression and determine the stability of 24 symptoms, five dimensional categories, and three subtypes over two episodes up to 20 years apart after adjusting for severity. They convincingly made the case that only the severity of anxiety and suicidal ideation were correlated and only to a moderate degree. They concluded that this finding would support a conception of unipolar depression as a single pleomorphic illness.

Our experience with the Systematic Treatment Enhancement Program for Bipolar Disorder Cohort raises a number of questions. We found that depression predicted suicidal ideation regardless of suicide attempt history but that anxiety and neuroticism predicted suicidal ideation only among those with a negative history of prior attempts. One of our collaborators, in examining anxiety comorbidity in this population, found that bipolar subjects with a lifetime history of anxiety disorder were more than twice as likely to have a lifetime history of suicide attempts as well. This raises the question of whether the two factors that Dr. Oquendo and colleagues found correlated across episodes might be confounded.

Dr. Oquendo et al. did not provide data on the frequency of prior attempts. Only 1.7% made an attempt during the study period. We found that among those with a history of prior attempts, poor role functioning and poor openness predicted suicidal ideation rather than anxiety and neuroticism and that extraversion was protective. It may be helpful in understanding the propensity for suicidal ideation to stratify by attempt history.

Joiner (2) postulated that attempting may lower the threshold for suicidal behaviors by sensitizing related cognitive structures and strengthening opponent processes. These, in turn, may contribute to the evolution of depressed states.

Dr. Oquendo et al. did not examine traits, such as neuroticism, that we find interacting with depression to influence suicidal ideation. Neuroticism, extraversion, and openness have been found to have both state and trait components, and we hope to examine the stability and contribution of such personality factors prospectively.

Finally, Dr. Oquendo et al. noted that these issues may have a bearing on the selection of acute and maintenance medication treatments. If anxiety and suicidal ideation are stable features, treatment must take account of that. We have suggested that distinguishing between negative and positive attempters provides a rationale for treatment selection in bipolar patients. Overall, aggressive treatment of depression appears warranted but also for attempters with the features mentioned, a focus on role functioning may minimize adverse experiences and reduce the risk of suicide. For nonattempters who fit this profile, more vigorous pharmacological treatment of anxiety and psychosocial treatment of neurotic thinking may be indicated.

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Dr. Oquendo and Colleagues Reply

TO THE EDITOR: We thank Drs. Allen and Chessick for their comments. Although there are similarities in the clinical presentation of bipolar depression and unipolar depression, neurobiological evidence from neuroimaging (1) and genetic studies (2) lends credence to the notion that unipolar and bipolar disorders are not the same. Thus, their data and ours are difficult to compare.

Nonetheless, they raise interesting points. They suggest an interaction between attempter status and predictors of suicidal ideation, with "anxiety, depression, and neuroticism" predicting suicidal ideation in nonattempters and "temperamental behavior, poor role functioning, and negative life events" predicting suicidal ideation among past attempters. This may well be the case, but is a different question from the one we examined in our article, namely, whether depressive symptoms are similar within subjects but across different episodes. The prediction of suicidal behavior is the focus of a recently published report in which we found that a history of suicide attempts, which was present in half of that group of depressed patients, predicts future suicidal behavior, as do pessimism and aggression/impulsivity (3).

The role of anxiety and depression in suicidal behavior appears to be complex. Some investigators found an association between anxiety and suicidal behavior in depressed individuals (4). We have previously reported that anxiety symptoms during a major depressive episode, and the presence of panic disorder that was comorbid with a major depressive episode in particular, appear to protect individuals against suicidal behavior (5). This is in agreement with the clinical presenta-